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Improving the interpretation of bone marrow imaging in cancer patients

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Abstract

Magnetic resonance imaging (MRI) is the best technique for bone marrow imaging. The MRI signal of bone marrow depends on the quantity of fat it contains and on its cellularity. Evaluation of marrow of patients treated for cancer is complicated by age and osseous site related changes in the distribution of normal haematopoietic (red) and fatty (yellow) marrow and by the changes induced by treatments: decrease in pathological cellularity, increase in fat proportion, conversion of red marrow to fatty marrow or, conversely, reconversion of fatty marrow in normal haematopoietic red marrow. The treatments used in oncology modify pathological marrow but also normal marrow and may sometimes lead to complications. These modifications may be focal or diffuse, homogeneous or patchy and symmetrical or asymmetric. The knowledge of bone marrow physiological status and post-therapeutic patterns is important for the interpretation of marrow disorders and effects of therapy and to avoid false-positive diagnosis of marrow metastases and tumour progression. The aim of this paper is to recall the MRI patterns of normal bone marrow and normal variations and to show the effects of treatments on bone tissue and normal bone marrow and treatment-related modifications on pathological marrow.

Keywords: Bone marrow; diagnostic imaging; cancer therapy.

Introduction

Several treatments used in oncology may induce changes in normal bone marrow and in pathologic marrow affected by diffuse or focal pathology. All these changes can be monitored on magnetic resonance (MR) imaging, which is the best method for the imaging of normal and pathologic marrow. MR evaluation of bone marrow is complicated by age-related changes and variants of normal and by changes induced by treatments.

Normal bone marrow

Normal bone marrow contains fat, haematopoietic cells and a fine mesh of reticulin in proportions varying according to age and the part of the bone under

consideration. On T1-weighted MR images, marrow signal increases when the percentage of fat increases. It decreases when the percentage of other cells increases.

According to the region of the skeleton and to the part of the bone examined, haematopoietic marrow contains 25%–70% cells with a longer T1 than fat. The greater the cellularity of the marrow, the lower the T1 MR signal intensity.

The distribution of haematopoietic marrow and its cellular content vary with age^[1]: haematopoietic marrow decreases and fatty marrow increases conversely. This physiological phenomenon is called conversion. It begins in the extremities and progresses toward the axial skeleton. At birth and in small children, bone marrow is entirely active throughout the skeleton and has a low signal on T1-weighted MR images. In young children, the diaphyses of long bones still contain haematopoietic

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marrow. Then conversion progresses from the diaphysis to the metaphyses. The epiphysis undergoes a more rapid conversion. In the vertebral bodies conversion begins around the vascular axis. The adult pattern is obtained at about 25 years. At this stage, the signal of fatty marrow in the peripheral skeleton is as intense as that of subcutaneous fat. The signal is less intense in the upper femoral metaphyses and in the pelvic bones, in which cellularity averages 50%. The signal of the vertebral bodies, which contain the richest marrow, is slightly lower than that of the pelvis (but higher than the signal of the intervertebral disk and muscles). In older subjects, the number of cells decreases as the quantity of fat increases. A progressive increase in signal intensity should therefore be observed in areas containing red marrow, such as vertebral bodies, as the subjects grow older.

Variants in marrow conversion

Conversion is not always homogeneous, it can be traduced by a heterogeneous signal, in a vertebral body for example, with cellular areas of hypointense signal mixed with fatty areas of intense signal. Benign regenerative medullary hyperplasia is the most frequent variant of the distribution of red marrow. It is due to chronic hypoxia (smokers) or anaemia (runners). It results in areas of hyposignal on T1-weighted images in the metaphysis of the long bones (close to the knee). The multiple and bilateral aspects allow the diagnosis.

Effects of radiation on normal bone marrow

Radiation induced changes in normal bone marrow

Early and late bone marrow changes during and after radiation therapy

Radiation treatment induces changes on normal marrow situated in the radiation field in patients treated for breast cancer, pelvic cancer, and Hodgkin's disease. Early and late bone marrow changes are seen on MR imaging. After radiation therapy, the signal intensity of normal bone marrow depends on the dose delivered and the interval between the treatment and the MR study. During the first 2 weeks after the start of therapy the signal intensity of the bone marrow on T1-weighted images decreases, apparently reflecting early bone marrow oedema with areas of increased signal intensity on short time inversion recovery (STIR) images. After 3 weeks, fatty replacement begins, the marrow shows an increasingly heterogeneous signal and, in the vertebral body, the signal from central marrow fat becomes prominent on T1-weighted images. Six weeks after therapy, there are two distinct types of late marrow patterns: homogeneous fatty replacement or a band-like pattern (sandwich vertebral body). Marrow

regeneration is more likely to occur in children than adults and when a large volume of marrow is irradiated than when radiation therapy is localized^[2]. A progressive decrease in T1-weighted image signal intensity indicates vertebral marrow recovery. Bone marrow which received more than 30 Gy is definitely damaged and exhibits a fatty signal on MR images. This pattern is due to decreased cellularity associated with loss of bone trabeculae^[3].

Changes after extensive radiation therapy

In patients who received extensive radiation therapy, the reconversion phenomenon occurs in the non-irradiated skeleton. Consequently, a diffuse hyposignal of normal red marrow (T1-weighted) should not be interpreted as diffuse infiltration. Reconversion in proximal femora is often observed in patients with sub-total irradiation: signal intensity of this reconversion is always greater than that of muscles.

Radiation induced complications

Radiation therapy may cause changes in the skeletal system depending on the age of the patient, absorbed dose, size of the radiation field, beam energy, and fractionation^[4,5].

Bone growth disturbances may be observed after irradiation of the immature and growing skeleton and are greater in younger patients or at puberty and with high doses. In children, epiphyseal changes can occur with doses as low as 400 cGy.

Osteoradionecrosis (OR) is usually diagnosed within 2–3 years after treatment and appears to be dose-related. MRI shows that uncomplicated OR is not accompanied by a soft tissue mass. The differential diagnosis includes osteomyelitis, recurrent primary disease, and radiation-induced second malignancies. The majority of cases of OR occur in the mandible, clavicle, humeral head, ribs and femur.

Pathologic fracture and collapsed vertebral body are frequently associated with OR. Recent collapsed vertebral bodies shows a low signal intensity on T1-weighted images (oedema) and therefore cannot be differentiated from malignant infiltration. Other MR sequences are useful to characterize a benign fracture.

Stress fractures on the sacral bone may occur after radiation therapy for pelvic cancers.

Avascular necrosis of the femoral head is most often associated with corticosteroid administration but has also been described following radiation therapy.

Radiation induced neoplasms

Benign tumours

Osteochondroma is the most common benign radiation-induced tumour. It occurs in about 12% of children

treated by radiation therapy under the age of 2 years. Any bone within the treatment field may be affected. Most lesions appear within 5–8 years after therapy. Radiation-induced osteochondroma are histologically and radiologically identical to osteochondroma that arise spontaneously.

Radiation-induced sarcomas

Osteosarcoma is the most common type of second malignant neoplasm. The radiation dose is usually greater than 30 Gy. Children are more susceptible to tumour induction. Radio-induced sarcomas arise after a long latency period (average 11–14 years), in both pre-existing bone lesions or in normal bones included in the radiation field. The new tumour is histologically distinct from the original lesion.

Effects of chemotherapy on normal bone marrow

Chemotherapy changes on normal bone marrow

During the first days after initiation of chemotherapy a decrease in the signal intensity of haematopoietic marrow is observed on T1-weighted MR images together with an increase in signal intensity on T2-weighted images, reflecting an increase in free water because of marrow congestion. Within a week, chemotherapy causes a myeloid depletion. The decrease in marrow cellularity leads to an increase in fatty content: an increase signal intensity is observed on T1-weighted images and a hypointense signal intensity on fat-suppression sequences.

After 3–4 weeks, haematopoietic recovery occurs with a reconversion of fatty to red marrow in the opposite way to marrow conversion, that is, from the axial to the appendicular skeleton. Because of regenerating red marrow, signal intensity decreases on T1-weighted images, first in the vertebral bodies, then in the pelvic bones and in the upper femoral metaphysis. T2-weighted and enhanced T1-weighted images allow areas of regenerating red marrow to be distinguished from malignant infiltration. Normal regenerating red marrow does not exhibit a marked increase in signal intensity in T2-weighted images and no enhancement after contrast injection. On out-of-phase gradient echo images, one can see a drop in signal intensity from normal haematopoietic marrow and no change in signal from malignant cells^[6]. Furthermore, islands of haematopoietic cells are generally bilateral and symmetric.

Complications of chemotherapy

Chemotherapy may be responsible for skeletal effects, particularly methotrexate osteopathy (bone pain, osteope-

nia and pathological fractures) occurring after long-term treatment with low dose or treatments with high-dose methotrexate. Nephrotoxicity of ifosfamide can lead to hypophosphataemic rickets. After intensive chemotherapy granulocytopenic patients can develop multifocal osteomyelitis. Bone infarction appearing after systemic or intra-arterial chemotherapy may mimic tumour progression^[7].

Bone marrow transplantation

Knowledge of the normal MR pattern of marrow regeneration after transplantation may be useful in screening for residual marrow disease, determining marrow engraftment, and differentiating marrow repopulation with normal versus malignant cells. Within 3 months after transplantation, T1-weighted MR images of vertebral marrow showed a characteristic band pattern consisting of a peripheral zone of intermediate signal intensity adjacent to the vertebral end-plates (regenerating haematopoietic cells) with a central zone of bright signal intensity (fatty marrow) which may be explained by the repopulation of the marrow around the capillary network adjacent to the vertebral end-plates^[8].

Effects of haematopoietic growth factor

Granulocyte colony-stimulating factor (G-CSF) is used to stimulate myeloid cell production in patients undergoing aggressive chemotherapy. It gives rise to a recolonisation of the fatty marrow by red marrow. Clinical data must always be taken into account for the interpretation of MR studies in these patients.

A diminished signal on T1-weighted images and a mildly increased signal on T2-weighted and STIR images are MR findings consistent with reconversion of yellow to red marrow. The changes may be homogeneously diffuse, simulating a marrow-infiltrative tumour, or focal and patchy, simulating metastases^[9]. They may be more prominent in the metaphyses, and are usually symmetrical but their distribution may be asymmetric^[10]. Awareness of this finding is important in order to avoid a false-positive diagnosis of marrow metastases or tumour increase^[11] and biopsy procedure^[12].

Effects of corticosteroid

Prolonged corticosteroid therapy leads to osteoporosis with fatty replacement and vertebral collapse. Avascular necrosis may occur in patients who have undergone bone marrow transplantation or prolonged steroid therapy and also after radiation therapy. The risk is major when corticosteroid and radiotherapy are associated. The most frequently affected regions are the hips, shoulders, and knees. MR imaging is sensitive for detection of early

ischemic necrosis. T1-weighted images show decreased signal intensity in the femoral head, often in a ban-like configuration. T2-weighted images may show a “double-line” sign of a high signal intensity rim. MRI is indicated in symptomatic patients with normal plain film.

Effects of biphosphonates

Biphosphonates are used as adjuvant therapy for the treatment of tumour-induced hypercalcaemia and metastatic bone pain and for the prevention of the complications of multiple myeloma and metastatic bone disease. Bisphosphonates are potent inhibitors of tumour-induced osteoclast-mediated bone resorption. Dynamic contrast enhanced MRI is effective for the monitoring of bone metastases response in patients receiving biphosphonates^[13]. Cases of osteonecrosis of the jaw associated with biphosphonate use have been reported^[14]. The condition causes chronic pain, dysfunction and disfigurement. No treatment has proven consistently effective. Concomitant chemotherapy and corticosteroid treatment, in particular, may result in immunosuppression and thereby predispose to ongoing local sepsis after minor trauma.

Effects of treatments on pathologic bone marrow

Effect of chemotherapy or radiotherapy on bone metastases

Tumours in bone marrow respond to treatment with a reduction in size (best demonstrated on T1-weighted images) and a change in signal intensity often better appreciated on T2-weighted or STIR images. When treatment is effective, a fatty halo may appear, marking a decrease in tumour size. When, after radiation therapy, the marrow becomes completely fatty, there is no lesion left. Most often, after radiation or chemotherapy, lesions are still visible. The differentiation between fibrosis and viable tumour is not possible, and imaging is not recommended to evaluate treatment effectiveness^[15].

In a large series, Brown *et al.*^[16] reported that T1-weighted MR response assessment, based on changes in size and number of vertebral metastases, accurately predicted progression of disease in 79% of cases and stable disease in 75% of cases, but did not predict regression of disease. Gadolinium-enhanced MR imaging with fat suppression sequences may be a useful method for assessing the effectiveness of therapy for spinal metastases. In a series of 62 vertebral bodies, Sugimura *et al.*^[17] observed a considerable diminution of lesion enhancement in responding lesions, after irradiation or chemotherapy.

Effect of therapy on disseminated bone marrow involvement: lymphomas, leukaemias, myelomas

Interpretation of post-treatment MRI changes can be difficult as there is a wide spectrum of possible treatment-induced changes on MRI depending on the pattern of bone marrow infiltration.

Lymphomas and leukaemias

When treatment is efficient, the signal intensity of the involved marrow increases as pathological cellularity decreases and the pathological enhancement after injection of contrast medium decreases on T1-weighted images. MR seems to have little role in the routine evaluation of the bone marrow in leukaemia. It could be useful in patients suspected of relapse, in case of bone pain with normal plain radiograph or in patients at high risk of relapse in whom serial bone marrow biopsies are negative^[18].

In multiple myelomas, an increased marrow signal is usually observed on post-treatment T1-weighted images due to replacement of tumour cells by fat cells. Response patterns associate normal aspects of bone marrow or persistent marrow abnormality, without contrast enhancement or only a peripheral rim enhancement^[19,20]. Local radiation therapy induces a decrease in lesion size and a central necrosis.

Conclusion

MR is the best imaging technique for assessing normal and pathologic bone marrow, to evaluate response during and after treatment and for the diagnosis of bone marrow relapse and complications. It can contribute greatly to guided biopsy. Radiologists should be aware of the MR patterns of normal bone marrow, of the aged-related changes, variants of normal and the pitfalls. Knowledge of therapy-related changes and post-therapeutic patterns allows them to be differentiated from residual or recurrent disease and misinterpretations avoided.

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